PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Overactive bladder symptom severity is associated with falls in community-dwelling adults: LOHAS study
AUTHORS	Fukuhara, Shunichi; Kurita, Noriaki; Yamazaki, Shin; Fukumori, Norio; Otoshi, Kenichi; Sekiguchi, Miho; Onishi, Yoshihiro; Takegami, Misa; Ono, Rei; Horie, Shigeo; Konno, Shin-ichi; Kikuchi, Shin-ichi

VERSION 1 - REVIEW

REVIEWER	Camille P. Vaughan, MD, MS Investigator, U.S.Dept. of Veterans Affairs, Birmingham/Atlanta Geriatric Research, Education, and Clinical Center Assistant Professor, Emory University, Dept of Medicine, Division of General Medicine & Geriatrics Atlanta, GA USA
REVIEW RETURNED	18-Dec-2012

GENERAL COMMENTS	The authors present findings from a cross-sectional study of community-dwelling older adults to assess the association between overactive bladder (OAB) symptoms and self-reported falls within the past month. The manuscript is well written and the authors have clearly detailed the study design and findings. While there is some evidence regarding the association of nocturia and urinary incontinence with falls, there is little evidence regarding overactive bladder, as a composite syndrome, and the association with falls. The addition of information related to symptom severity and the population attributable fraction analysis (including information related to functional mobility with the TUG) and depression) make this manuscript unique in the literature. While there are significant missing data, the authors have addressed this limitation with the sensitivity analyses presented. The reviewer has a few minor comments related to clarifying the wording of a few sentences in the Discussion and a question regarding the analysis: Page 12, lines 31-35 - While significant cognitive impairment would make it difficult to complete a questionnaire (unless a caregiver was able to assist), the comment that those with cognitive impairment wouldn't attend a health check-up exam seems out of place. Please present evidence to this effect or consider re-wording the sentence. Page 13, lines 17-22 - The comment that physicians should be cautious about asking their patients who have fallen about OAB symptoms could be re-worded to encourage providers to ask about urinary symptoms. I think the authors meant that physicians should ask patients who have a history of falling about OAB symptoms, but

	to do this in a sensitive way? Page 13, line 28 - The authors suggest that urgency could cause individuals to lose focus while walking. Did the authors look at urgency as an isolated symptom from the OABSS to see if was associated with fall risk?

REVIEWER	Alayne D. Markland Associate Professor of Medicine/Geriatrics Department of Veterans Affairs University of Alabama at Birmingham, Birmingham, AL USA Grant funding from the Dept of VA and NIH.
REVIEW RETURNED	21-Jan-2013

THE STUDY	The research question is not clearly defined in the introduction, but is clearly defined in the Abstract. Cause and effect is implied in the title and key messages -- this should be revised. Please see additional comments below on the participants and conditions.
RESULTS & CONCLUSIONS	The 6 subgroup analyses for the dependent variable along with adjusted models are limited by sample size and wide CIs.
REPORTING & ETHICS	STROBE data needed to describe the cohort.
GENERAL COMMENTS	In this community-based survey of Japanese residents aged 40 years and older who completed health check-ups in 2010, 1350/2505 had OAB symptoms scores and data on “any” falls and frequent falls, defined as ≥2 falls in the last month. After adjusting for mobility problems (“locomotive dysfunction”) and depressive symptoms, the participants with mild or moderate OAB symptoms had higher rates of “any” fall and frequent falls. In the adjusted data from Table 2, participants with mild and moderate OAB symptoms had greater odds of having any or more frequent falls. Participants with longer TUG test times and depressive symptoms had significantly higher odds of having any fall or frequent falls in separate multivariable models. However, the data from these tables and the sample size numbers do not suggest that the three independent variables (OAB symptoms, TUG tests, and Depressive symptoms) were used in the same model. The interactions between OAB symptoms, mobility, and depressive symptoms are not clearly defined and identified. Overall, the paper presents interesting data showing an association with increased OAB symptoms severity and falls. The data presented on locomotive dysfunction and depressive symptoms related to falls, but does not relate to OAB symptoms. Table 2 should be revised to include the interaction of the TUG test and the depressive symptoms in the model including OAB symptoms. Sample size is not consistent in all the data presented. The title suggests a cause and effect relationship and should be revised. Gender differences should also be compared. Cause and effect is implied in the conclusion statement from the abstract and in the text. Comments by section: 1. Article focus – difficult to describe “how much” or the “contribution” of OAB symptoms had on falls. The analysis performed can only comment on an association or correlation. The prevalence fraction of OAB symptoms were not directly compared with “locomotive dysfunction” and depressive symptoms. Separate models were used for comparison. Please revise these statement of comparison. 2. In the introduction, please be more specific for your definition of

	"locomotive dysfunction" and it is was used in your study cohort. What other physical and mental contributors were used? These terms are broad and need more specific examples used to define the study objective. 3. Methods – Please mention more data on why the 6 "mutually exclusive" categories were used to define OAB severity. Is the TUG test the only test used to define "locomotive dysfunction?" Can you comment on the cut-off values of the TUG test in adults < 60 years of age? Please define "frequent falls" more consistently. Is it >2 or ≥2 falls in the previous month? Were all co-morbid diseases assessed by self-report other than hypertension and diabetes? In the statistical section, relative risks and odds ratios are used interchangeably. Please define which was used in the multivariable models. Does the subgroup analysis using the 6 OAB groups as the dependent variable in the models have significant power to detect the differences when adjusting for other independent variables – wide CI noted for the sub-group analyses? Please comment on the goodness of fit of the models. The high rate of missing data needs to be mentioned as a limitation. 4. Results – See comments above regarding the 3 multivariable models presented in Table 2 and Table S3. 5. Discussion – Please better define PAPF estimates for the reader. Also, please comment on the missing data and the potential gender differences in OAB symptoms. The comments regarding the treatment of OAB symptoms and improvement in falls is only speculative –please mention that further work is needed in this area.

VERSION 1 – AUTHOR RESPONSE

Comment 1:
The authors present findings from a cross-sectional study of community-dwelling older adults to assess the association between overactive bladder (OAB) symptoms and self-reported falls within the past month. The manuscript is well written and the authors have clearly detailed the study design and findings. While there is some evidence regarding the association of nocturia and urinary incontinence with falls, there is little evidence regarding overactive bladder, as a composite syndrome, and the association with falls. The addition of information related to symptom severity and the population attributable fraction analysis (including information related to functional mobility with the TUG) and depression) make this manuscript unique in the literature. While there are significant missing data, the authors have addressed this limitation with the sensitivity analyses presented. The reviewer has a few minor comments related to clarifying the wording of a few sentences in the Discussion and a question regarding the analysis: Page 12, lines 31-35 - While significant cognitive impairment would make it difficult to complete a questionnaire (unless a caregiver was able to assist), the comment that those with cognitive impairment wouldn't attend a health check-up exam seems out of place. Please present evidence to this effect or consider re-wording the sentence.

Response: While no clear evidence has indicated that those with cognitive impairment do not attend a health check-up exams, we have found that elderly individuals with cognitive impairment are less likely to participate in epidemiological studies. [1] We therefore reworded the text as follows: "individuals with cognitive impairment are unlikely to participate in epidemiological studies and complete self-reported questionnaires." (page 13, lines 34-38)

Comment 2:
Page 13, lines 17-22 - The comment that physicians should be cautious about asking their patients who have fallen about OAB symptoms could be re-worded to encourage providers to ask about urinary symptoms. I think the authors meant that physicians should ask patients who have a history of falling about OAB symptoms, but to do this in a sensitive way?

Response: In accordance with the reviewer's suggestion, we have re-worded the text as follows: "they

should be sensitive when asking patients about their experiencing any OAB symptoms" (page 14, lines 32-38)

Comment 3:
Page 13, line 28 - The authors suggest that urgency could cause individuals to lose focus while walking. Did the authors look at urgency as an isolated symptom from the OABSS to see if was associated with fall risk?

Response: As we did not examine urgency as an isolated symptom from the OABSS, we re-worded the text as follows: "more frequent walking to the bathroom may raise the risk of falling. In addition, urgency may cause individuals to lose focus while walking due to nocturia or frequency, rendering them more susceptible to falling" (page 14, lines 45-49)

RESPONSE TO REVIEWER Alayne D. Markland:
We wish to express our appreciation to the Reviewer for his or her insightful comments, which have helped us significantly improve the paper.

Comment 1:
The research question is not clearly defined in the introduction, but is clearly defined in the Abstract. Cause and effect is implied in the title and key messages -- this should be revised. Please see additional comments below on the participants and conditions.

Response: While we agree that cause and effect cannot be drawn from our cross-sectional study, as we already described as a limitation in the article summary and discussion section, several reports have noted that the contribution of exposure on outcome was estimated using the estimated prevalence fraction from cross-sectional studies, assuming a causal relationship between the exposure and the outcome. [2] Therefore, in the revised manuscript, we have amended the text to reflect our view that "potential" contribution of each exposure (OAB symtoms, mobility problems, and depressive symptoms) was estimated using PAFs [formerly "PAPFs"], assuming a causal relationship between each of the exposures and the falls.

We revised the title as follows: "Overactive bladder symptom severity is associated with falls in community-dwelling adults: LOHAS study".

In addition, we revised the article summary as follows: "Here, we assessed the relationship between overactive bladder symptom severity and falls and estimated the potential contribution of overactive bladder symptoms on falls among community-dwelling individuals, assuming a causal relationship between OAB symptom and falls." (page 4, lines 20-24)

Comment 2:
STROBE data needed to describe the cohort.

Response: Although we would like to describe the cohort profile in detail, the manuscript length limit of 4,000 words prevents us from doing so; as such, we added the following sentence to the revised manuscript: "Details of the design of the LOHAS have been reported previously." [3] (page 6, lines 18-20)

Comment 3:
In this community-based survey of Japanese residents aged 40 years and older who completed health check-ups in 2010, 1350/2505 had OAB symptoms scores and data on "any" falls and frequent falls, defined as ≥2 falls in the last month. After adjusting for mobility problems ("locomotive dysfunction") and depressive symptoms, the participants with mild or moderate OAB symptoms had higher rates of "any" fall and frequent falls. In the adjusted data from Table 2, participants with mild and moderate OAB symptoms had greater odds of having any or more frequent falls. Participants with longer TUG test times and depressive symptoms had significantly higher odds of having any fall or frequent falls in separate multivariable models. However, the data from these tables and the sample size numbers do not suggest that the three independent variables (OAB symptoms, TUG tests, and Depressive symptoms) were used in the same model.

Response: As the reviewer mentions, we did conduct separate logistic regression analyses for any fall or frequent falls. However, in each analysis, we included all three independent variables (OAB symptoms, TUG tests, depression symptoms). We erroneously reported the number of participants absent for depressive symptoms in Table 2 as 2,038 (1,141 is correct) and thank the reviewer for pointing out this mistake.

Comment 4:
The interactions between OAB symptoms, mobility, and depressive symptoms are not clearly defined and identified.

Response: As described in the method, the primary exposure in this study was OAB symptoms. Therefore, we additionally examined the potential effect modification of TUG, depressive symptoms, and gender difference on the association between OAB symptom severity and any fall or frequent falls over the previous month. Overall, testing for the presence of any of the three interaction pairs (the product terms of OAB symptoms severity with gender, TUG, or depressive symptoms) produced no statistically significant results. Text on this point has now been appended to the methods and results sections.

Comment 5:
Overall, the paper presents interesting data showing an association with increased OAB symptoms severity and falls. The data presented on locomotive dysfunction and depressive symptoms related to falls, but does not relate to OAB symptoms. Table 2 should be revised to include the interaction of the TUG test and the depressive symptoms in the model including OAB symptoms.

Response: As replied previously, we noted no apparent interactions and have therefore not revised Table 2 (except for correcting the number of participants).

Comment 6:
Sample size is not consistent in all the data presented.

Response: As replied previously, we corrected the number of the participants in Table 2.

Comment 7:
The title suggests a cause and effect relationship and should be revised.

Response: As replied previously, we revised the title.

Comment 8:
Gender differences should also be compared.

Response: As replied previously, we assessed potential gender differences (effect modification) and found none.

Comment 9:
Cause and effect is implied in the conclusion statement from the abstract and in the text.

Response: As replied previously, we agree that cause and effect cannot be drawn from our cross-sectional study and have already touched on this point as a limitation in the article summary and discussion section. Therefore, we revised the conclusion statement from the abstract as follows: “OAB symptoms might be important contributors to falls among community-dwelling adults”. In addition, we also revised the conclusion statement in the text as follows: “OAB symptoms might have a similar or greater contribution to falls than mobility problems or depressive symptoms”

Comment 10:
Article focus – difficult to describe “how much” or the “contribution” of OAB symptoms had on falls. The analysis performed can only comment on an association or correlation. The prevalence fraction of OAB symptoms were not directly compared with “locomotive dysfunction” and depressive symptoms. Separate models were used for comparison. Please revise these statement of comparison.

Response: As replied previously, while we agree that cause and effect cannot be drawn from our cross-sectional study, several reports have noted that the contribution of the exposure on outcome was estimated using the estimated prevalence fraction from cross-sectional studies, assuming a causal relationship between the exposure and the outcome. [2]

We have therefore revised the article summary as follows: “Here, we assessed the relationship between overactive bladder symptom severity and falls and estimated the potential contribution of overactive bladder symptoms on falls among community-dwelling individuals, assuming a causal relationship between OAB symptom and falls.”

As for the comparison of the prevalence fractions, we apologize for the data error in Table 2 which may have led to misinterpretation of our logistic regression models. As replied previously, Table 2 includes the results of identical (i.e. not separate) logistic regression models including all three independent variables (OAB symptoms, TUG tests, and depression symptoms) for any fall and frequent falls, respectively. Therefore, we were able to compare the size of PAFs (formerly “PAPFs”) of each of the three independent variables estimated from the same model as that used in the literature. [2]

Comment 11:
In the introduction, please be more specific for your definition of “locomotive dysfunction” and it is was used in your study cohort. What other physical and mental contributors were used? These terms are broad and need more specific examples used to define the study objective.

Response: We apologize for using ambiguous phrases such as locomotive dysfunction, physical contributors, or mental contributors. The LOHAS study aims to evaluate the risk of cardiovascular disease, quality of life, medical costs, and mortality attributable to “locomotive syndrome”, a term proposed by the Japanese Orthopedic Association. [3] Locomotive syndrome is characterized as a set of associated symptoms occurring in response to problems of the locomotive systems. [4] This concept has now been described in the cohort statement of the methods section.

As for other contributors, we did not analyze any variables other than ones described in this manuscript. We have therefore revised the study objective in the introduction as follows: “We also assessed the potential contribution of OAB symptom severity to falls in the population.”

In addition, we also revised the statement regarding mobility problems (formerly “locomotive dysfunction”) and depressive symptoms in the methods section as follows: “In addition to accounting for the contribution of OAB symptoms to falls, we considered the contributions of mobility problems (i.e. problems in gait, balance, and mobility) and depressive symptoms as well, citing these parameters as secondary exposures in light of their prevalence in aging societies and their predictability of fall risk in the literature.” (page 7, lines 10-16)

Comment 12:
Methods – Please mention more data on why the 6 “mutually exclusive” categories were used to define OAB severity. Is the TUG test the only test used to define “locomotive dysfunction?” Can you comment on the cut-off values of the TUG test in adults < 60 years of age? Please define “frequent falls” more consistently. Is it >2 or ≥2 falls in the previous month?

Response: In accordance with the reviewer’s suggestion, we have revised the methods section regarding the definition of the categories as follows:

“A total OABSS score of 3 or more and an urgency score of 2 or more is the recommended cut-off for diagnosing OAB, and the severity is further divided into mild (total score of 3 to 5 points), moderate (6 to 11 points), and severe (12 or more points), according to Japanese clinical practice guidelines. Therefore, individuals with a total OABSS score of 2 or less or an urgency score of 1 or less are considered to be “non-OAB.” To assess the dose-response relationship of the strength of the association between OAB symptom severity and falls citing non-OAB individuals with a total score of 0 as reference, participants with and without OAB were divided into six categories based on severity of total OABSS score and distribution of the participants: non-OAB with 0, 1, 2, or 3 or more points;

mild OAB; and moderate to severe OAB. The median and range of total OABSS score among the six groups are described in Table 1, along with the number of participants." (page 6, lines 36- page 7, lines 7)

The TUG test was the only test used to define "locomotive dysfunction" in this article. In accordance with the reviewer's suggestions, we have now replaced "locomotive dysfunction" with "mobility problems."

Although no reference TUG values have been established for persons aged 40 to 59 years, we believe "5.5 to 8.1 s" is a feasible range, as a previous study found the mean TUG value to be 5.5 s in healthy young adults (mean age: 22.3 years) and 8.1 s in adults aged 60 to 69 years, the mean for this group as described in the original manuscript. [5]

In accordance with the reviewer's suggestion, we added the value of "≥2" to mentions of "frequent falls" in the revised manuscript.

Comment 13:
Were all co-morbid diseases assessed by self-report other than hypertension and diabetes?

Response: Yes. In the "measurement of potential confounding variables" portion of the methods section, we replaced "via questionnaire" with "via self-reported questionnaire."

Comment 14:
In the statistical section, relative risks and odds ratios are used interchangeably. Please define which was used in the multivariable models.

Response: In accordance with the reviewer's suggestion, we removed the term "relative risks" and retained "odds ratios" and re-worded the sentence as follows: "Effect measures in the present study were odds ratios (ORs) of the three exposures for any fall and frequent falls estimated using logistic regression models"

Comment 15:
Does the subgroup analysis using the 6 OAB groups as the dependent variable in the models have significant power to detect the differences when adjusting for other independent variables – wide CI noted for the sub-group analyses?

Response: Because OAB is the main exposure in this study, we did not conduct subgroup analyses stratified by the 6 OAB categories.

Comment 16:
Please comment on the goodness of fit of the models. The high rate of missing data needs to be mentioned as a limitation.

Response: The goodness of fit of the covariate-adjusted logistic models in the primary analyses was assessed using the Hosmer-Lemeshow test, and a description of this process and its results were appended to the methods and results sections. However, this test could not be conducted during the sensitivity analyses because it is not applicable to data imputed multiple times. In accordance with the reviewer's suggestion, we mentioned the high rate of missing data in the primary analyses in the limitations section of the discussion. [6]

Comment 17:
Results – See comments above regarding the 3 multivariable models presented in Table 2 and Table S3.

Response: Please see previous replies regarding the logistic regression models presented in Table 2.

Comment 18:
Discussion – Please better define PAPF estimates for the reader. Also, please comment on the missing data and the potential gender differences in OAB symptoms. The comments regarding the treatment of OAB symptoms and improvement in falls is only speculative –please mention that further

work is needed in this area.

Response: In accordance with the reviewer's suggestion, we described the definition and interpretation of PAF (formerly "PAPF") in the methods section:

"In general, in a cross-sectional study, the PAF is the fraction of the prevalent outcomes that would be prevented if a certain exposure were removed. In other words, if the exposure were removed, then some fraction of the outcomes could be prevented, and that fraction is the PAF. For this study, the outcomes used were both "any fall" and "frequent falls," and the exposures used were OAB symptom severity, mobility problems, and depression symptoms. One assumption of this computation is that there is an unconfounded, causal relation between the exposure(s) and the outcome(s)." (page 9, lines 25-35)

As replied previously, we commented on the missing data in the limitation paragraph.

In addition, we added the following sentences to the discussion:

"no gender differences were apparent in the relationship between OAB symptoms and falls"

"Further study is needed to clarify whether or not treatment of OAB symptoms is associated with reduction of falls." (page 14, lines 27-29)

References

1. Jacomb PA, Jorm AF, Korten AE, et al. Predictors of refusal to participate: a longitudinal health survey of the elderly in Australia. BMC Public Health 2002;2 doi: 4 10.1186/1471-2458-2-4.
2. Sousa RM, Ferri CP, Acosta D, et al. Contribution of chronic diseases to disability in elderly people in countries with low and middle incomes: a 10/66 Dementia Research Group population-based survey. The Lancet 2009;374:1821-30
3. Otani K, Takegami M, Fukumori N, et al. Locomotor dysfunction and risk of cardiovascular disease, quality of life, and medical costs: design of the Locomotive Syndrome and Health Outcome in Aizu Cohort Study (LOHAS) and baseline characteristics of the study population. J Orthop Sci 2012;17:261-71 doi: 10.1007/s00776-012-0200-5 [doi].
4. Nakamura K. Locomotive syndrome: disability-free life expectancy and locomotive organ health in a "super-aged" society. J Orthop Sci 2009;14:1-2 doi: 10.1007/s00776-008-1302-y [doi].
5. Brotherton SS, Williams HG, Gossard JL, et al. Are measures employed in the assessment of balance useful for detecting differences among groups that vary by age and disease state? J Geriatr Phys Ther 2005;28:14-9
6. StataCorp. Stata Multiple-Imputation Reference Manual Release 11. College Station, TX: StataCorp, LP, 2009.

VERSION 2 – REVIEW

REVIEWER	Markland, Alayne UAB Medical Centre
REVIEW RETURNED	11-Mar-2013

GENERAL COMMENTS	Will defer to editors on the inclusion of a STROBE diagram describing the analytic sample of this cohort study